Refractory Hypotension

Diagnosis and Management in Surgical Patients

LOUIS L. SMITH, *M.D.*, and BRUCE W. BRANSON, *M.D.*, Los Angeles

Two KINDS of circulatory collapse are seen most frequently in acutely ill surgical patients. One is due to acute reduction of blood volume following loss of blood, plasma or extracellular fluid. This situation is obvious and specific replacement is required. Response is prompt and recovery is the rule providing the cause of the circulatory collapse can be corrected. Circulatory failure of this kind can be called "responsive hypotension."

The other kind of circulatory collapse occurs in surgical patients who, although they seem to have a normal blood or plasma volume, do not have adequate circulation. Frequently such persons because of the obscure nature of the vascular collapse, are given intravenous vasopressor agents. Their response to resuscitative efforts is sluggish, and the mortality rate is high. "Refractory hypotension" is an apt term for circulatory failure of this type.

In the present discussion of the possible causes and treatment of refractory hypotension, we have avoided the term "shock" because of confusion regarding its definition and because it is frequently used in the experimental laboratory to describe a circulatory collapse in which death is considered to be inevitable. Hypotension, for the purpose of this discussion, will refer to those clinical conditions in which the pulse rate is accelerated, the blood pressure low and there is evidence of impaired perfusion of vital organs.

ETIOLOGY

The following case illustrates the problem of refractory hypotension in a postoperative patient.

A 53-year-old Caucasian housewife entered the hospital for elective operation on the biliary tract because of pain in the right upper quadrant of the abdomen. She had had jaundice, which had subsided without medical treatment. A cholecystogram was reported as showing a nonfunctioning gallblad-

• Refractory hypotension is circulatory collapse of obscure cause which occurs in surgical patients who are thought to have a normal blood volume but in whom adequate circulation cannot be maintained. Such patients are usually treated empirically by the administration of intravenous vasopressor agents, and the mortality rate is relatively high.

A specific diagnosis of the underlying cause for the refractory hypotension can be made by thorough clinical evaluation. Specific treatment aimed at correcting the underlying cause of the vascular collapse will lower the mortality rate in this serious type of circulatory failure.

der. At operation the gallbladder was observed to contain many stones and there was a solitary gallstone in the common duct, which was dilated. The ampulla of Vater would not admit a No. 3 Bakes dilator and there was a cholecystduodenal fistula.

The operative procedure consisted of cholecystectomy, choledocholithotomy, closure of the cholecystduodenal fistula and transduodenal sphincteroplasty. On the first postoperative day the patient had a temperature of 102.2° F. The pulse rate was 88 and the blood pressure 120/88 mm. of mercury. The hematocrit was 44 mm. (before operation it was 38 mm.).

On the afternoon of the first postoperative day, the patient attempted to go to the bathroom but collapsed on the floor in her room. Soon afterward the blood pressure was unobtainable and no radial pulse could be felt. Abdominal palpation revealed no tenderness. The hematocrit was reported as 49 mm. Intravenous Aramine® (metaraminol) drip administration was begun and the blood pressure rose to 65/50 mm. Intravenous corticosteroid administration (Solu-Cortef® 300 mg.) did not elevate the low blood pressure further. On the morning of the second postoperative day the temperature rose to 103.8° F., the blood pressure and the pulse became unobtainable. The patient was digitalized with Cedilanid,® intravenous administration of tetracyline hydrochloride (Achromycin®) was begun and the concentration of Aramine increased in order to restore the blood pressure. As the response was poor, drip administration of norepinephrine was begun. The hematocrit at this time was 55 mm. The pa-

tient's condition deteriorated rapidly and she died on the morning of the second postoperative day.

At autopsy, acute pancreatitis with extensive retroperitoneal edema and fat necrosis was noted. There was a focal area of hemorrhage within the head of the pancreas.

In this case, the cause of vascular collapse was not recognized during life and plasma volume replacement was not carried out.

The causes for hypotension in surgical care are few. Common conditions which can produce vascular collapse are: Concealed hemorrhage, cardiovascular catastrophe, pulmonary catastrophe, invasive sepsis, electrolyte disorder, postoperative pancreatitis, vascular impairment of bowel, acute adrenal insufficiency.

Concealed Hemorrhage: One of the commonest causes for unexplained circulatory failure following operation is concealed hemorrhage. This diagnosis is frequently obscure in the early stages before the development of abdominal distention and flank dullness. Continued tachycardia or hypotension responsive to transfusion, a falling hematocrit or bleeding from drain tubes should make one suspicious of this complication.

Cardiovascular Catastrophe: The cardiovascular causes for circulatory failure are well known. Pulmonary embolism, coronary occlusion, or acute cardiac arrhythmias may be responsible for refractory hypotension. In all of these disorders the blood volume is normal and hypotension is the result of "pump failure."

Pulmonary Catastrophe: Disturbances in pulmonary ventilation must be considered as possible etiological factors in the production of refractory hypotension. Undiagnosed pneumothorax or airway obstruction produce vascular collapse by asphyxia. Spreading pneumonia not only impairs pulmonary ventilation but poses the threat of blood stream invasion by the infectious agent.

Sepsis with Blood Stream Invasion: Refractory hypotension may also be brought about by spreading infection with bacteremia or septicemia. Whether the septic process be peritonitis, enterocolitis or pneumonia makes little difference. The acute inflammatory process is associated with the development of inflammatory edema and subsequent reduction of the plasma volume. Additional whole blood volume may be sequestered in congested vessels within the area of acute inflammation. As a result of this inflammatory process there is a reduction of the plasma volume or effective whole blood volume.

Electrolyte Disorders With or Without Acid-Base Changes: Acute surgical illness is frequently associated with significant losses of electrolyte-rich body fluids through depletion of extracellular plasma volume. When these losses reach a critical point, compensatory mechanisms fail and circulatory collapse ensues. Knowledge of the pressor effect of the sodium ion is important in understanding the pathologic biochemical features of hypotension. This pressor effect is evidently lost by either hyponatremia or sodium deficit even though the two may not occur together. An electrolyte disorder should be considered in any patient with hypotension who also has altered cerebration or neuromuscular irritability or muscular weakness.

Acute electrolyte disorders are frequently associated with acid-base shifts which in themselves may be responsible for altered cardiovascular function. Abnormal breathing or a change in respiratory rate is indicative of acid-base disorders. The usual acid-base change in patients with refractory hypotension is a metabolic acidosis, frequently combined with respiratory acidosis.[8,9] The metabolic acidosis develops from the accumulation of acid metabolites during a period of low perfusion of tissues and obligatory anaerobic glycolysis. Clinical and experimental observations indicate that there is a diminished response to intravenous sympathicomimetic agents in patients or experimental animals with acidosis.[5,10,11] This diminished response is most noticeable with respect to myocardial function.

Respiratory acidosis frequently occurs with the induction of anesthesia and in prolonged operations, particularly within the chest.[2] This acid-base defect can be associated with disturbances in cardiovascular function such as acute cardiac arrhythmia.[6] Maier and coworkers observed a high incidence of postoperative hypotension in patients with severe respiratory acidosis (blood pH less than 7.1).[6] Cardiac arrhythmia is most likely to occur on the sudden return to breathing of room air following a period when the patient has been subjected to high concentrations of carbon dioxide with its associated respiratory acidosis.[3,7]

Acute Pancreatitis: The great masquerader of the upper abdomen is acute pancreatitis. The sudden onset of circulatory collapse may be the first evidence that this disease is present. Several mechanisms predispose to circulatory failure in this condition. One is the extensive loss of plasma in the retroperitoneal tissues due to the acute inflammatory process. A second is the sequestration of whole blood in acutely congested blood vessels in the area of acute inflammation. Still another is the loss of protein-rich fluid into the peritoneal cavity as a result of the acute peritonitis. The net result of these factors is a reduction in the plasma volume and a decrease in the effective circulating whole blood volume. This disease should always be suspected

when unexplained circulatory failure follows any operation, but particularly following biliary or gastric operation.

Vascular Impairment of the Bowel: One of the most insidious causes of refractory hypotension is intestinal obstruction due to mesenteric vascular occlusion. There may be vague abdominal symptoms early in the illness and the radiologic observations may be equivocal. The first sign that bowel infarction exists is the onset of vascular collapse. Prompt diagnosis and definitive operation are essential for survival.

Acute Adrenal Insufficiency: Refractory hypotension in a patient with a history of tuberculosis or the presence of advanced malignant disease raises the possibility of acute adrenal insufficiency due to the destruction of the gland or replacement by tumor tissue. The widespread use of corticosteroid drugs in the management of a variety of chronic medical diseases poses an additional problem of recognizing relative adrenal insufficiency. A history of recent steroid therapy should alert the examining physician to the possibility of vascular collapse due to this cause.

DIAGNOSIS

In dealing with refractory hypotension, critical evaluation is needed to establish an accurate diagnosis and to institute specific therapy. Often a detailed history and physical examination will elicit additional information that may explain the circulatory failure. Table 1 outlines laboratory studies that are helpful in determining the cause of unexplained hypotension. Several points should be emphasized in regard to the use of these studies.

Blood: Serial hematocrit or hemoglobin determinations frequently demonstrate evidence of loss of plasma or extracellular fluid. A rising hematocrit or hemoglobin value indicates plasma loss, the cause of which must be determined by further clinical evaluation. Acute hemorrhage is not associated with an immediate drop in the hematocrit or hemoglobin value, since transcapillary refilling of the plasma volume must take place before the reduced red cell mass can be diluted. Serial determinations of hemoglobin and cell volume are essential if this change is to be demonstrated.

Plasma electrolyte determinations should be obtained if change in cerebration, evidence of neuromuscular irritability or unexplained hypotension develops. In prolonged surgical illnesses in which oral intake of fluids or food has been impossible or there has been excessive loss of fluids and electrolytes through nasogastric or fistula drainage, it is well to make determinations frequently to insure the adequacy of replacement therapy.

TABLE 1.—Suggested Diagnostic Studies In Unexplained Hypotension

A. BLOOD:
    Serial hematocrit or hemoglobin determinations
    Plasma electrolyte content
    Carbon dioxide content
    Amylase content
    Cultures

B. X-RAY OBSERVATIONS:
    Postero-anterior film of chest
    Plain film of abdomen
    Lateral decubitus film of abdomen

C. ELECTROCARDIOGRAM

D. ADRENAL CORTICAL EVALUATION:
    Eosinophil count
    Plasma corticosteroid concentration
    "Corticosteroid infusion test"

In clinical situations in which the initial carbon dioxide combining power is abnormally high or low or the patient has acute and unexplained respiratory changes, determination of the pH and the total carbon dioxide content of the arterial blood is most helpful in establishing an accurate diagnosis of the acid-base disorder which may be present. A pH determination is necessary to indicate whether a low carbon dioxide combining power is due to metabolic acidosis or respiratory alkalosis.

Serum amylase determination is another helpful diagnostic test in unexplained hypotension. A rising hematocrit or hemoglobin value following operation on the biliary tract or the stomach is an indication for the measurement of amylase activity, particularly if there is evidence of circulatory failure.

The onset of temperature elevation followed by vascular collapse is evidence of bloodstream infection and is indication for obtaining multiple blood cultures. The more cultures drawn, the more likely is identification of the organism. Then sensitivity studies can make antibiotic treatment more effective.

X-ray Observations: X-ray examination of the chest and abdomen is frequently helpful in establishing the cause of unexplained hypotension. Unsuspected pneumothorax, pneumonia or bowel obstruction may be demonstrated. Occasionally it is possible to see free intraperitoneal air or fluid levels on the lateral decubitus view of the abdomen.

Electrocardiogram: It is advisable to obtain an electrocardiographic tracing on all patients with unexplained vascular collapse and to interpret it with care. S-T segment changes and nonspecific T wave changes can occur as a result of myocardial ischemia following the onset of a hypotensive incident.

Adrenal Cortical Evaluation: Acute adrenal cortical insufficiency can be diagnosed by actual measurement of the plasma corticosteroid levels* or by an eosinophil count. The presence of a normal num-

*The term corticosteroid is used herein to mean 17-OH corticosteroid.

ber of circulating eosinophils in a patient with circulatory stress is evidence of adrenal insufficiency. If serious question exists that adrenal failure may be the cause of the vascular collapse, the administration of intravenous hydrocortisone as an "infusion test" should promptly solve the problem. This test will be discussed later in this paper.

MANAGEMENT

The aim of treatment in refractory hypotension is the restoration of adequate perfusion to vital organs at the earliest possible time. Blood pressure alone does not always reflect the status of organ perfusion or capillary circulation. One must consider the mental status of the patient, vital organ function (such as urinary output) and the general clinical appearance. The following treatment routine has been found helpful in restoring circulatory homeostasis in problem cases.

Correction of Electrolyte Disorders: Any demonstrable electrolyte disorder should be corrected, particularly any evident deficit of the sodium ion. Acute losses of sodium are frequently associated with extracellular fluid volume reduction in surgical patients. One must be careful to distinguish acute sodium deficit from a low plasma sodium concentration of dilutional origin produced by over-administration of electrolyte-free solution during the post-traumatic period of antidiuresis.

We have observed beneficial results by the administration of concentrated sodium solutions to patients with refractory hypotension who had low plasma sodium concentrations.[9] The use of hypertonic saline solutions (3 per cent or 5 per cent sodium chloride) allows the correction of acute sodium deficiency without the administration of excess water. The coexistence of hyponatremia and metabolic acidosis makes sodium bicarbonate or lactate the ideal repair solution. One cannot postulate that all patients in shock will benefit by the use of concentrated sodium salts. The sodium therapy must be matched to the particular deficit observed in each instance.

Correction of Acid-Base Disorders: As previously mentioned, the two commonest disorders of acid-base balance in patients with refractory hypotension are metabolic acidosis and respiratory acidosis.[8,9] Sodium bicarbonate or lactate is useful in correcting any existing metabolic acidosis. It should be borne in mind, however, that the administration of base cannot be expected to restore a normal hemodynamic state in the presence of an uncorrected deficit in blood volume. Following adequate blood volume restoration, the correction of

an associated metabolic acidosis in a patient with refractory hypotension might be expected to improve cardiovascular function.

The most important aspect of dealing with respiratory acidosis is preventing it. Adequate ventilation during long and extensive operations, encouraging coughing and deep breathing in the postoperative period, and endotracheal suctioning, particularly in thoracic operations, will help to minimize the threat of respiratory acidosis. Respiratory acidosis is usually difficult to treat once it develops, for there is usually some underlying acute or chronic pulmonary disease process such as pneumonia or emphysema. The judicious use of tracheostomy where indicated, and of positive pressure assisted respiration, offer the best chance of improvement.

Control of Sepsis: In the case of vascular collapse as a concomitant of severe sepsis, vigorous and prompt control of the infection by a combination of well-established surgical principles and intensive antibiotic therapy offer the best chance for survival. Broad spectrum antibiotics should be administered in high concentration by the intravenous route since intramuscular antibiotics may not be absorbed during the period of acute vascular collapse. Administration of whole blood or plasma until the venous pressure [monitoring of central venous pressure is discussed later in this presentation] begins to show an elevation has been helpful in restoring circulatory homeostasis in some of these patients. A critically ill patient with severe sepsis and vascular collapse may show a favorable response to overtransfusion.[4]

Blood Volume Restoration: Whole blood and plasma are the most important therapeutic agents in the treatment of refractory hypotension. Although one must be concerned about overtransfusion and congestive heart failure, elderly patients in vascular collapse are as vulnerable to prolonged under-replacement of blood as they are to sudden overtransfusion. Colloid replacement must be accurately tailored to the apparent volume requirements of the patient. The object of this therapy should be to restore not only the blood pressure but the flow of blood to vital organs.

Corticosteroid Administration: The diagnostic tests for establishing adrenal cortical insufficiency have been outlined. In clinical situations in which urgency demands that it must be determined quickly that adrenal insufficiency is not the cause of vascular collapse, the "corticosteroid infusion test" can be used. Solu-Cortef in a dosage of 100 to 300 mg. can be administered intravenously in 500 cc. of normal saline solution. Signs of circulatory improvement should promptly become evident if adrenal insufficiency is the cause.

"CONSTANT MONITORING" OF CENTRAL VENOUS PRESSURE

ZERO AT LEVEL OF PATIENT'S RT. AURICLE
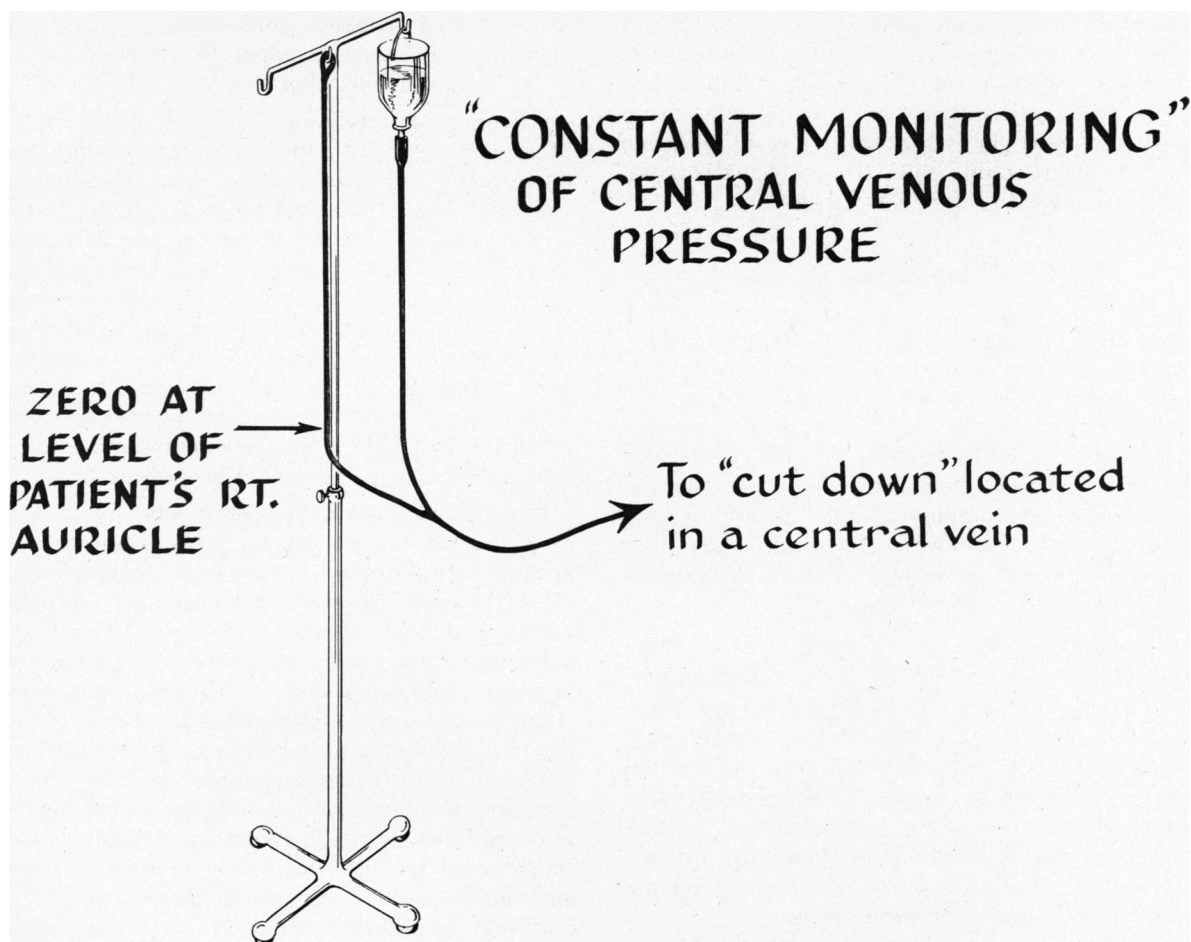
To "cut down" located in a central vein

Figure 1.—Diagram of a simple disposable venous pressure set.* One vertical limb of the plastic Y is taped to the intravenous standard on which is placed an adhesive tape scale with zero at the estimated level of the right auricle of the heart. The second vertical limb of the plastic Y is connected to a bottle of normal saline solution and serves as a reservoir for filling the "manometer" limb of the apparatus. Following filling the "manometer" with saline solution, the reservoir side is clamped and the column of saline solution is allowed to seek the level of the patient's venous pressure. Such measurements can be made as often as desired and serve as a constant monitor of myocardial function relative to blood volume replacement.

Clinical studies by Anderson and coworkers[1] indicated that in certain situations, particularly bloodstream infection, the administration of pharmacological doses of hydrocortisone may attenuate the cardiovascular effect of the septic process. The dose in this case would approach a gram per day and would be continued for a short time only, then gradually tapered until discontinued. Such intensive therapy awaits further clinical and experimental evaluation. The use of this potent drug is not without serious complications and should be resorted to only when conventional therapy has failed to restore adequate circulation.

Vasopressor Therapy: The use of the potent vasopressor drugs in the management of circulatory collapse has been the source of considerable contro-

versy. In elderly patients we have found these drugs useful to maintain blood pressure until specific therapeutic measures have restored adequate circulation. Patients under general or regional anesthesia with diffuse circulatory paralysis likewise respond well to the temporary use of vasopressor drugs.

The apparent improvement in blood pressure following the use of these potent drugs should not lull the surgeon into complacency. The underlying cause for the circulatory collapse must be determined. Every effort should be made to institute specific therapy and to discontinue the administration of vasoconstrictor agents at the earliest possible moment.

Care should be taken not to produce an acute dilutional hyponatremia by the over-administration of 5 per cent dextrose in water relative to the concentration of vasoconstrictor being used. The fluid

volume administered should be closely observed and the concentration of vasoconstrictor drug increased when fluid intake exceeds actual body requirements.

GUIDES IN TREATMENT

The objective of the therapeutic program to be used in patients with circulatory collapse is the maintenance of adequate perfusion to vital centers and the restoration of circulatory homeostasis at the earliest possible time. Several indices are helpful in the management of these patients. These include observation of the state of consciousness, vital signs and hourly urinary output, monitoring the central venous pressure and the serial determination of the hematocrit or hemoglobin. An alert patient with adequate urinary output is not in serious danger even though the blood pressure may have fallen. By contrast an elderly hypertensive patient who is stuporous and oliguric is in immediate danger even though the blood pressure may still be within a normotensive range.

In acute circulatory disturbances the production of urine usually reflects the status of the blood volume. If there is a blood volume deficit, oliguria ensues. Hence the value of the hourly urinary output in determining whole blood or plasma volume deficits in refractory hypotension. A rising hourly urine output concomitant with colloid administration indicates favorable progress in restoring the blood volume. The urine output should range between 30 and 60 cc. per hour.

Central venous pressure is another helpful guide in determining the adequacy of colloid administration in patients with refractory hypotension. A polyethylene catheter (the size of a 14 gauge needle) is placed in a large arm vein and inserted to the axillary or subclavian level. The venous pressure is then measured at frequent intervals by observing the height of a column of saline solution in the vertical limb of a disposable venous pressure set. Zero is at the estimated level of the right auricle. Figure 1 shows such a venous pressure set.* Colloid administration can be safely continued as long as the venous pressure remains stable. A rising venous pressure indicates overexpansion of blood volume relative to myocardial function. In such a situation, the rate of transfusion must be curtailed and the patient digitalized; or, if the patient's condition has become stabilized, consideration should be given to venesection. In our experience, the serial observation of the central venous pressure has been more helpful in determining the colloid requirement of patients with refractory hypotension than has actual measurement of the blood volume, which all too fre-

* Available from the Fenwal Laboratories, Framingham, Massachusetts.

quently shows the volume to be normal or increased, yet the patient remains in circulatory collapse.

DISCUSSION

There is a growing tendency to consider circulatory collapse or shock as a primary diagnosis rather than to recognize it for what it is—a sign of a serious underlying complication. Too frequently a patient with refractory hypotension is considered to be in "irreversible shock." It should be pointed out that no clinical test or criteria are available to determine when a patient has become refractory to all therapy, and "irreversible" therefore has no place in clinical service except possibly in viewing such a problem case in retrospect.

Circulatory collapse as we see it on the clinical service is different from that produced in the laboratory. This condition frequently occurs in elderly arteriosclerotic patients with degenerative diseases involving multiple organs. This is in contrast to the healthy laboratory animal with no degenerative or significant arteriosclerotic changes. The presence of diffuse arteriosclerosis makes specific treatment imperative and requires greater vigilance during therapy if the patient is to survive.

Loma Linda University School of Medicine, 1700 Brooklyn Avenue, Los Angeles 33 (Smith).

REFERENCES

1. Anderson, G. V., and Marshall, K.: Septic abortion with vascular collapse, West. J. Surg. Obstet. and Gyn., in press.
2. Beecher, H. K.: Acidosis during thoracic surgery, J. Thor. Surg., 19:50, 1950.
3. Brown, E. B., Jr., and Miller, F.: Ventricular fibrillation following rapid falling alveolar carbon dioxide concentration, Am. J. Physiol., 169:56-60, 1952.
4. Ebert, R. V.: Discussion of Septic Shock at the Conference on Recent Progress and Present Problems in the Field of Shock, Walter Reed Army Hospital, Washington, D. C., Dec. 14-17, 1960.
5. Houle, D. B., Weil, M. H., Brown, E. B. Jr., and Campbell, G. S.: Influence of respiratory acidosis on ECG and pressor responses to epinephrine, norepinephrine and metaraminol, Proc. Soc. Exp. Biol. and Med., 94:561-564, 1957.
6. Maier, H. C., Rich, G. W., and Eichen, S.: Clinical significance of respiratory acidosis during operations, Ann. Surg., 134:653-658, 1951.
7. Miller, F. A., Brown, E. B. Jr., Buckley, J. J., Vanbergen, F. H., and Varco, R. L.: Respiratory acidosis: Its relation to cardiac function and other physiologic mechanisms, Surg., 32:171-183, 1952.
8. Smith, L. L., Hamlin, J. T. III, Walker, W. F., and Moore, F. D.: Metabolic and endocrinologic changes in acute and chronic hypotension in man, Metabolism, 8:862, 1959.
9. Smith, L. L., Ball, M. R., and Moore, F. D:. Clinical and biochemical observations in refractory hypotension in man. Submitted for publication to Annals of Surgery.
10. Thrower, W. B., Darby, T. D., and Aldinger, E. E.: Acid-base derangements and myocardial contractility, Arch. Surg., 82:56, 1961.
11. Weil, M. H., Houle, D. B., Brown, E. B., Campbell, G. S., and Heath, C.: Influence of acidosis on the effectiveness of vasopressor agents, Circulation, 16:949, 1957.